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(54) Title: PHENOL AND PYRIDINOL DERIVATIVES AS LUSITROPIC AGENTS

(57) Abstract

Fused aryl derivatives are described as lusitropic agents for use in the treatment of cardiovascular disease where there is a component of diastolic failure.

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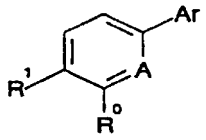
Phenol and pyridinol derivatives as lusitropic agents.

The present invention relates to the use of certain fused aryl derivatives as lusitropic agents in the treatment of cardiovascular diseases where there is a component of diastolic failure.

WO 91/17987 discloses fused aryl derivatives as agonists of a cyclic AMP-dependent protein kinase.

It has now been found that these derivatives enhance myocardial relaxation i.e. have positive lusitropic activity and are therefore of use in the treatment of cardiovascular diseases where there is a component of diastolic failure.

Accordingly in a first aspect the present invention provides the use of a compound of the formula (1) :



Formula (1)

or a pharmaceutically acceptable salt thereof, wherein :

A is N or CH

R^0 is OH or a bioprecursor thereof,

R^1 is A^0CO_2H, $P(X)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or a bioprecursor thereof,

A^0 is a single bond, CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

R^2 is phenyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkyl-C_{1-4}alkyl, or C_{1-8}alkyl optionally substituted by C_{1-4}alkoxy,

R^3 is H, methyl or ethyl,

R^4 is H or C_{1-3}alkyl,

R^5 and R^6 are each C_{1-3}alkyl or together form a 1,2-ethanediyl group or 1,3-propanediyl group,

X is O or S and

Ar is 1-naphthyl optionally substituted in the 4-position by hydroxy or C_{1-6}alkoxy, 2-naphthyl optionally substituted in the 1-position by hydroxy or C_{1-6}alkoxy, 3-phenanthryl, 9-phenanthryl, 2-quinolinyl, 4-quinolinyl, 3-thianaphthenyl or 2-benzofuranyl in the manufacture of a medicament having positive lusitropic activity.

In a second aspect the present invention provides a method of enhancing myocardial relaxation which comprises administering to a host in need thereof an effective amount of a compound of formula (1) as hereinbefore defined or a pharmaceutically acceptable salt thereof.

In a third aspect the present invention provides a method of treating cardiovascular disease where there is a component of diastolic failure which comprises administering to a host in need thereof an effective amount of a compound of formula (1) as hereinbefore defined or a pharmaceutically acceptable salt thereof. Examples of such diseases include congestive heart failure, angina, hypertension and cardiomyopathy (Kenakin et al., J. Pharmacol. Exp. Ther. 1991, 257, 1189-1197).

Examples of compounds of the formula (1) and suitable substituent values are as disclosed in WO 91/17987.

Preferably R^1 is P(O)(OH)(OR^2) or a bioprecursor thereof as defined in WO 91/17987.

Particular compounds of the formula (1) include :

ethyl pivaloyloxymethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate,

6-(2-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-[2-(1-pentyloxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

4-ethoxy-4-oxo-1,3,4-dioxyphosphono[5,6-b]-7-(1-naphthyl)pyridine, and

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate.

Compounds of the formula (1) can be prepared and administered as pharmaceutical compositions as described in WO 91/17987.

The positive lusitropic effect of the compounds of the formula (1) can be demonstrated by measurement of cardiac muscle relaxation time in rabbit ventricle.

Papillary muscles from the right ventricle of female Albino New Zealand rabbits were mounted in standard organ baths containing oxygenated Krebs solution. One end of the muscle was connected to an isometric transducer which allowed recording of contractile force and its first derivative on chart recorders. Test compounds were added to the bath in a cumulative manner. Relaxation time was calculated as the time taken from peak tension to the point of half relaxation. At concentrations of 30-300 μM, and stimulation rates at 0.5, 1 or 2 Hz, the following test compounds caused a 5-30% decrease in the relaxation

time indicating a positive lusitropic effect of use in the treatment of cardiovascular diseases where there is a component of diastolic failure as hereinbefore described.

Compounds tested include:

ethyl pivaloyloxymethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate,

6-(2-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

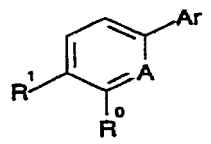
6-[2-(1-pentyloxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

4-ethoxy-4-oxo-1,3,4-dioxyphosphono[5,6-b]-7-(1-naphthyl)pyridine, and

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate.

Claims :

1. The use of a compound of the formula (1) :



Formula (1)

or a pharmaceutically acceptable salt thereof, wherein :

A is N or CH

R^0 is OH or a bioprecursor thereof,

R^1 is A^0CO_2H, $P(X)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or a bioprecursor thereof,

A^0 is a single bond, CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

R^2 is phenyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkyl-C_{1-4}alkyl, or C_{1-8}alkyl optionally substituted by C_{1-4}alkoxy,

R^3 is H, methyl or ethyl,

R^4 is H or C_{1-3}alkyl,

R^5 and R^6 are each C_{1-3}alkyl or together form a 1,2-ethanediyl group or 1,3-propanediyl group,

X is O or S and

Ar is 1-naphthyl optionally substituted in the 4-position by hydroxy or C_{1-6}alkoxy, 2-naphthyl optionally substituted in the 1-position by hydroxy or C_{1-6}alkoxy, 3-phenanthryl, 9-phenanthryl, 2-quinolinyl, 4-quinolinyl, 3-thianaphthenyl or 2-benzofuranyl in the manufacture of a medicament having positive lusitropic activity.

2. A method of enhancing myocardial relaxation which comprises administering to a host in need thereof an effective amount of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

3. A method of treating cardiovascular disease where there is a component of diastolic failure which comprises administering to a host in need thereof an effective

amount of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

4. The use according to any one of claims 1 to 3 wherein R^1 is $P(O)(OH)(OR^2)$ or a bioprecursor thereof.

5. The use according to any one of claims 1 to 3 wherein the compound of the formula (1) is selected from :

ethyl pivaloyloxymethyl[6-(1-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]phosphonate,

6-(2-naphthyl)-3-(5-tetrazolyl)pyridin-2(1H)-one,

6-[2-(1-pentyloxy)naphthyl]-3-(5-tetrazolyl)pyridin-2(1H)-one,

4-ethoxy-4-oxo-1,3,4-dioxyphosphono[5,6-b]-7-(1-naphthyl)pyridine, and

ethyl 2-methoxy-2-[6-(2-naphthyl)-2-oxo-1,2-dihydro-3-pyridyl]propionate.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/44; A61K31/675

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	WO,A,9 117 987 (SMITH KLINE AND FRENCH LABORATORIES LIMITED) 28 November 1991 cited in the application see the whole document especially page 1, line 9-line 21 and examples 1,30,33,35 and 68 ---	1-5
P,Y	WO,A,9 206 085 (SMITH KLINE AND FRENCH LABORATORIES LIMITED) 16 April 1992 see page 1, line 9 - page 1, line 23 see page 18, line 20 - page 19, line 7 see page 21, line 17 - page 21, line 32 ---	1-5

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 MAY 1993	1. 06. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MAIR J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS vol. 257, no. 3, June 1991, pages 1189 - 1197 KENAKIN T.P. ET AL 'THE RELATIVE EFFICIENCY OF BETA ADRENOCEPTOR COUPLING TO MYOCARDIAL INOTROPY AND DIASTOLIC RELAXATION: ORGAN-SELECTIVE TREATMENT FOR DIASTOLIC DYSFUNCTION' cited in the application see the whole document ---	1-5
A	EP,A,0 406 958 (JANSSEN PHARMACEUTICA N.V.) 9 January 1991 see the whole document especially page 16 line 10-32 ---	1-5
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 33, no. 6, June 1990, pages 1735 - 1741 COATES, W.J. ET AL '1,4-BIS(3-OXO-2,3-DIHY DROPYRIDAZIN-6-YL)BENZENE ANALOGUES: POTENT PHOSPHODIESTERASE INHIBITORS AND INODILATORS.' see the whole document -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/00615

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claimm 1 and 2 are directed towards a method of treatment of the human /animal body the search has been carried out and based upon th e alleged effects of the compounds.

2. [X] Claims Nos.: 1-4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds wich are theoretically defined by the general formula of claim 1 the search has been restricted to those compounds specifically mentioned in the description and claims and the general concept of the invention.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300615
SA 71579

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 24/05/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9117987	28-11-91	AU-A-	7871791	10-12-91
		EP-A-	0532531	24-03-93
WO-A-9206085	16-04-92	AU-A-	8543191	28-04-92
EP-A-0406958	09-01-91	AU-B-	623539	14-05-92
		AU-A-	5879890	10-01-91
		CN-A-	1051560	22-05-91
		JP-A-	3063277	19-03-91
		CA-A-	2020630	08-01-91
		US-A-	5043327	27-08-91
		US-A-	5120845	09-06-92